## R E M A R K S

Claim Amendments

The feature of claim 10 was introduced into claim 8.

Entry of this amendment is respectfully requested, since the amendment to claim 10 involves a feature that was set forth in the claims prior to the final rejection.

Presently Claimed Invention

The presently claimed invention is directed to a method of treating a disease of a posterior segment of an eye comprising administering subconjunctivally to a patient an effective amount for treatment of an injection comprising fine particles containing a drug and enabling the drug concentration in a retina-choroid to be sustained, the disease of the posterior segment of the eye being uvetis, cytomegalovirus retinitis, age-related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy or retinal detachment, the fine particles containing the drug being a matrix-type, wherein the drug is

dispersed uniformly in the fine particles, a particle diameter of fine particles being 50 nm to 150 μm and the fine particles being made of a biodegradable polymer or a biosoluble polymer.

Obviousness Rejections under 35 USC 103

Claims 8, 10, 12 and 18 were rejected under 35 USC 103 as being unpatentable over Peyman (USP 6,395,294) in view of Wong et al. (USP 5,869,079) for the reasons stated on pages 2 to 5 of the Office Action.

It was admitted in the Office Action that Peyman does not teach that the fine particles are of the matrix type as recited in applicants' claim 8.

Claims 8, 10, 12, 18 and 19 were rejected under 35 USC 103 as being unpatentable over Peyman (USP 6,395,294) in view of Wong et al. (USP 5,869,079) and further in view of Hata et al. (USP 6,264,970) or Weiner et al. (USP 5,466,233) for the reasons stated on pages 5 to 6 of the Office Action.

It was admitted in the Office Action that Peyman and Wong et al. do not teach polylactic acid having a weight-average

molecular weight of 20,000 as recited in applicants' claim 19.

The position was taken in the Office Action that Wong et al. teach compositions and methods of biodegradable implants that provide a controlled, sustained drug release and that the implants are preferably monolithic having the active agent homogeneously distributed through the polymeric matrix, such as polylactide, while Peyman does not teach that the fine particles are of the matrix type. Therefore, it was concluded in the Office Action that it is obvious to combine the known method of treating and porduct of Peyman with the technique of making a matrix-type particle of Wong et al. with predictable results.

The applicants disagree with the above position and conclusion for the following reasons and assert that the presently claimed invention patentably distinguishes over the references.

One of Ordinary Skill in the Art Would Not Consider to Combine Peyman and Wong et al. to Arrive at the Presently Claimed Invention

Wong et al. teach an implant for sustained release comprising a drug such as dexamethasone, a release modulator such

as hydroxypropylmethylcellulose, and a polymer such as a polyester of lactic acid and glycolic acid (see claim 1 of Wong et al.). Further, Wong et al. teach that the release rate of the drug can be modulated by addition of the release modulator to the implant (see column 2, lines 29 to 31 of Wong et al.). Wong et al. also teach that formulations of a hydrophobic drug with biodegradable matrixes may have a release profile which shows little or no release until erosion of the matrix occurs (see column 1,lines 25 to 28 of Wong et al.). Moreover, Wong et al. actually appreciate that drug release begins in four weeks after initiation for an implant made with dexamethasone and a polymer (polylactic acid polyglycolic acid) ("PLGA") (i.e., a release modulator-free implant) (see column 8, lines 45 to 47 and Fig. 1A of Wong et al.). That is, Wong et al. suggest that the release modulator is an essential element for releasing a drug promptly and sustainably when the implant is made with a drug and a polymer.

On the other hand, the objective of the presently claimed invention is to provide a sustained drug delivery to the posterior segment of an eye by subconjunctival injection (see the

last paragraph on page 3 of the present specification). Further, since the ultimate objective of the presently claimed invention is the treatment of a posterior segment disease (see applicants' present claims), the drug delivery system must release the drug promptly. That is, a drug delivery system which releases a drug four weeks after injection (as in Wong et al.) is not appropriate for treatment of a severe disease, such as a posterior segment disease of the eye.

Considering the above-discussed findings, when the presently claimed invention was made, it is respectfully submitted that a person of ordinary skill in the art would not consider to utilize fine particles containing a release modulator in order to develop a prompt and sustained drug delivery to the posterior segment of an eye. However, the present inventors discovered after intense investigations that a drug can be delivered to the posterior segment of an eye promptly and sustainably by subconjunctival administration of release modulator-free fine particles comprising a drug and a biodegradable or a biosoluble polymer (see the paragraph bridging pages 3 and 4; the last paragraph on page 13; and Table 1 on page 14 of the present specification).

Table 1 of the present specification is reproduced as follows:

Table 1: Betamethasone concentrations in retina-choroids (μg/g tissue)

| | Control group (suspension) | Microsphere injection |
|---|---|---|
| Two days after administration | 0.54±0.35 | 0.70±0.26 |
| Seven days after | 0.96±0.54 | 0.18 |
| 14 days after | ≦ Detection limit | 0.17±0.06 |
| 21 days after | ≦ Detection limit | 0.10±0.02 |
| 28 days after | ≦ Detection limit | 0.09±0.02 |

In view of the above, it is respectfully submitted that Wong et al. teach away from the presently claimed invention.

Wong et al. teach a monolithic implant having an active agent homogeneously distributed through a polymeric matrix, such as polylactide, and that a monolithic implant is usually preferred over an encapsulated implant, due to ease of manufacture (see column 5, lines 19 to 24 of Wong et al.).

However, Wong et al. merely exemplify a monolithic implant containing a release modulator, and Wong et al. do not teach or suggest release modulator-free fine particles, which are of a matrix type.

Further, Wong et al. teach that a reservoir type (i.e., a capsule-type) may be of benefit where the therapeutic level of the drug falls within a narrow window (see column 5, lines 19 to 20 of Wong et al.). Meanwhile, heretofore it has been known that it is difficult to sustain a drug concentration in the posterior segment tissues for a long period by subconjunctival injection (see the paragraph bridging pages 2 and 3 of the present specification), which means that the therapeutic level of a drug falls within a narrow window after a subconjunctival injection of the posterior segment of an eye. Furthermore, the objective of the presently claimed invention is to develop a sustained drug delivery to the posterior segment of an eye by a subconjunctival injection as described above (see the last full paragraph on page 3 of the present specification).

That is, when the presently claimed invention was made, it is respectfully submitted that a person of ordinary skill in the

art would choose a capsule-type, NOT a matrix-type, in order to attempt to arrive at the presently claimed invention. Even from this point of view, it is respectfully submitted that Wong et al. teach away from the presently claimed invention.

Therefore, it is respectfully submitted that it would not be obvious to a person of ordinary skill in the art to combine Peyman and Wong et al. to arrive at the presently claimed invention.

The Presently Claimed Invention Exhibits Advantageous Results which are Unpredictable from Peyman and Wong et al.

Peyman teaches a subconjunctival injection solution comprising drug-containing fine particles as a vitreous delineating agent. However, Peyman relates to a surgical method to alleviate a structural disorder (see claim 1 of Peyman). Further, Peyman does not teach or suggest whether posterior segment diseases of the eye can be treated with a subconjunctival injection solution.

On the other hand, the subconjunctival injection of drug-containing fine particles of the presently claimed invention inhibits choroidal neovascularization even 14 and 28 days after administration (see the paragraph bridging pages 16 and 17 and Table 2 on page 18 of the present specification), which means that the drug-containing fine particles of the presently claimed invention can treat a posterior segment disease of the eye without surgery.

Table 2 of the present specification is reproduced as follows:

Table 2: Neovascularization exhibition rates (%) of betamethasone-containing microsphere

| | Control group | Microsphere group |
|---|---|---|
| After 14 days | 60.9±4.4 | 12.5±2.4 |
| After 28 days | 73.4±6.0 | 12.5±2.4 |

As discussed hereinabove, Wong et al. teach that a reservoir type (i.e., a capsule-type) may be of benefit where the

therapeutic level of the drug falls within a narrow window (see column 5, lines 19 to 20 of Wong et al.). Furthermore, in the implant of Wong et al., the release rate of the drug is modulated by addition of a release modulator to the implant (see column 2, lines 29 to 32 of Wong et al.), and therefore appreciable drug release begins four weeks after initiation in the absence of the release modulator (see column 8, lines 45 to 47 and Fig. 1A of Wong et al.).

In contrast to Wong et al. and Peyman, the present inventors discovered that subconjunctival injection of matrix-type fine particles comprising a drug (betamethasone) and a biodegradable or a biosoluble polymer (such as polylactic acid) enables a drug delivery to the posterior segment of an eye (such as the retina-choroid) two days after administration, and a detectable concentration of the drug therein was maintained at least for 28 days (see the last paragraph on page 13 and Table 1 (which is reproduced hereinabove) on page 14 of the present specification). That is, a subconjunctival injection of matrix type fine particles of the presently claimed invention enables a drug delivery to a posterior segment of an eye, promptly and

sustainably in the absence of a release modulator.

It is respectfully submitted that the above results would be unexpected for a person of ordinary skill in the art. Consequently, it is respectfully submitted that the presently claimed invention exhibits advantageous results which are unpredictable from Peyman and Wong et al.

In view of the above, it is respectfully requested that the 35 USC 103 rejection of claims over Peyman in view of Wong et al. be withdrawn.

Applicants' Present Claims Patentably Distinguish Over Peyman in View of Wong et al. and Further in View of Hata et al. and Weiner et al.

The position was taken in the Office Action that Hata et al. (USP 6,264,970) and Weiner et al. (USP 5,466,233) teach preferable molecular weights of a polymer used for the fine particles of the presently claimed invention.

It is respectfully submitted that it has been demonstrated above that applicants' presently claimed invention patentably distinguishes over Peyman in view of Wong et al. Therefore, the teachings of polymer molecular weight in Hata et al. and Weiner

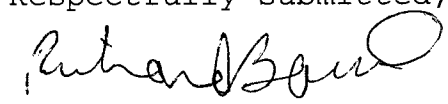
et al., when combined with the teachings of Peyman in view of Wong et al., would not lead one of ordinary skill in the art to the presently claimed invention.

Accordingly, withdrawal of the 35 USC 103 rejection of claims over Peyman in view o Wong et al. and further in view of Hata et al. and Weiner et al. is respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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